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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,518	07/06/2001	Keith D. Allen	R-716	3954

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,518	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32,36,38-40 and 42-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32,36,38-40 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-32, 36, 38-40 and 42-46 are pending in the application.

This Office Action is in response to the Amendment filed on 5/13/05.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/05 has been entered.

Response to Amendment

The rejection of claims 40 and 41 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 29-32, 36, 38-40 and 42-46 under 35 U.S.C. 101/112 1st paragraph is maintained for reasons set forth of the record mailed on 1/13/05 and further discussed below.

The specification is objected to for reasons given below.

Response to Arguments

Claim Rejections - 35 USC § 101

Claims 29-32, 36, 38-40 and 42-46 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

In response to this rejection, Applicant argues that the newly amended claims, drawn to a transgenic mouse having a CX2 null allele, has patentable utility according to utility guidelines set forth in MPEP because the claimed invention has a well-established utility and is useful for a particular practical purpose. Applicant assert that the skilled in the art would immediately appreciate how to use a knockout mouse because any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted gene regardless of specific phenotypes, characterizations or properties of the knockout mouse. Applicant further cites a passage at NIH website which indicate that knockout mice represent a critical tool in studying gene function. Furthermore, Applicant asserts that the newly amended claims drawn to transgenic mouse comprising null-reporter alleles "is an indispensable starting point for studying the function of every gene"(Austin et al., 2004), "is an invaluable tool for investigating gene function on a genomic scale"(Molecular biology of Cell, Albert, 4th ed., Garland Science (2002), "is a powerful tool to investigate directly the importance and function of the gene" (Genes VII, Oxford university 2000), "offers a powerful approach to study gene function in a mammalian organism," (Joyner, Gene targeting: A Practical Approach, Oxford University Press 2000), "has revolutionized our ability to study gene function in cell culture *in vivo*," (Matise, Production of Targeted Embryonic Stem Cell Clones), and "provide an important means for understanding gene function."(Crawley, what's wrong with my mouse behavioral phenotype of transgenic and knockout mice, Wiley-Liss 2000). Moreover, Applicant asserts that the knockout mouse have a clear, specific and unquestionable utility as with gas chromatographs, screening assays and nucleotide sequence techniques as taught by MPEP 2107.01,I. Moreover, Applicants indicates that the claimed invention is purchased by one large pharmaceutical company, and the database

comprising analysis of the claimed mouse is subscribed by Merck, Pfizer and GSK, thus such commercial acceptance more than satisfied the practical utility requirement of 101 and 112 1st paragraph according to *Brenner v. Manson* and *Phillips Petroleum Co. v. U.S. Steel Corp.*, and Lipscomb's Walker on Patents 5:17, p 562 (utility may be evidenced by sales and commercial demand). Furthermore, Applicant also asserts that the claimed invention is useful for a particular purpose since the mouse has specific disclosed phenotype. As such, the utility of the claimed mouse is apparent to one of skilled in the art because said mouse can be used to study the association between CX2 with such phenotype. Moreover, Applicant argues that the utility of the claimed inventions does not depend on a correlation between the disclosed phenotype and a disease in human according to *In re Brana*, and the knockout mouse with a specific gene disrupted is a widely accepted model for determine gene function (Austin and Doetschman) with well-established utility. Applicant asserts that the Federal court found that utility had been demonstrated because the claimed compound had activity against a murine tumor implanted in a mouse in *Brana*, which is similar to the instant case in which the knockout mouse with a specific gene disrupted is a widely accepted model. Applicant further argues that the observation and conclusions in the instant application are made by skilled artisans from Deltagen, all of whom hold MD's, DVM's with additional Ph.D, ACVP or ABP. In addition, Applicant argues that using CX2 knockout mouse to study the function of CX2 and association of CX2 and the disclosed phenotype is specific to this mouse. Further, Applicant asserts that studying the function of the CX2 is a substantial utility because there is no further research required to confirm the utility of the claimed mouse in determining CX2 function because 1) the value of the knockout mouse is well established in the art; 2) further characterization of the mouse itself if not

required to confirm its utility in studying the CX2 function. Moreover, Applicants argue that the phenotype is no longer recited in the claims, and all the mouse with null allele of CX2 would have the same phenotype, wherein the age and gender matched controls are used. In addition, Applicant asserts that the claimed mouse can be used to study gene expression since the null allele comprises a lacZ gene. Applicant thus concludes that the claimed invention has credible, substantial and specific utility which satisfies the statue of 35 U.S.C. 101.

These arguments have been fully considered but deemed unpersuasive. The reasons for the utility and non-enablement rejection were discussed in detail in the office action mailed on 1/13/05 and in the utility rejection discussed above. In response to Applicant's response regarding any knockout mouse has a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible." In the instant case, the utility that applies to any knockout mouse is not specific to the claimed invention, the CX2 transgenic mouse having a null allele. It was well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility, of which must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art as indicated by the quotations cited by

Applicant, for example, studying gene function. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial. The utility guidelines specifically state that further research is not a "substantial utility." The MPEP states "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved..." In this case, further study of mice would have been required to determine how to use the mouse of applicant's invention according to the embodiments described in the specification. Applicant's assertion that the claimed mouse is useful to study the association of CX2 with the phenotype is an invitation for further research on the claimed invention in which the function of said invention Applicant clearly does not know. Further study would also be required to determine the function of the disrupted gene. Furthermore, the overall phenotype of the claimed mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder, screening drugs and treatment for such disorder. Moreover, the phenotype of increased body weight, increased body length or increased body weight to body length ratio is not supported by the instant specification (see Figure 3, and discussion in office action mailed on 7/13/04). Thus, using the mice claimed for further research is not a "substantial utility." Furthermore, Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics

observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). As such, a knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using the claimed mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

In response to Applicant's argument of the commercial sale of the claimed mouse, Applicant is reminded that the sale of a product does not automatically gives the product patentable use according to the statue of 35 U.S.C.101 and the utility guideline set forth in the MPEP. Commercial success is only considered as secondary evidence for overcoming a 103 (a) rejection according to guidelines set by MPEP. *Brenner v. Manson* does not validate the notion that commercial use automatically gives a claimed product patentable utility. The purchase of the claimed mouse by a large pharmaceutical company neither proves commercial success of the claimed mouse nor does it gives the claimed mouse a patentable utility. The case law of *Phillips Petroleum Co. v. U.S. Steel Corp.* 6 USPQ 2d 1065 talks about commercial success in context as secondary consideration in favor of nonobviousness (see page 1096). It states "of course, there must be a nexus "between the merits of the claimed invention and the evidence offered if that evidence is to be given substantial weight enroute to conclusion on the obviousness issue."

Stratoflex , 713 F.2d at 1539 [218 USPQ at 879] (noting *Solder Removal Co. v. United States Intern. Trade* , 582 F.2d 628, 637 [199 USPQ 129, 137] (C.C.P.A. 1978)). Crystalline polypropylene is one of the most widely used chemical compositions in commerce today. Worldwide demand is presently approximately fourteen billion pounds, with the United States' demand totaling nearly six billion pounds per year. (Mark, Tr. at 503.) 68 Experts from both sides were in general agreement that crystallinity is the characteristic which gives polypropylene its immense commercial value." According to the case law, the commercial success is established by the worldwide use of the claimed compositions and the generation of high revenue from the sale of the claimed composition. However, the sale of the present claimed invention to one pharmaceutical company clearly does not mount to such "commercial success." The subscription of the database comprising data from the claimed invention to three pharmaceutical company does not mount to such "commercial success" as well because it is unclear whether and how the companies are going to use the data from the claimed invention. Applicant is reminded that subscription of a database is different from actually using the data obtained from the claimed invention, wherein the database presumably contains much more information other than that is related to the claimed invention. The case law of 9 USPQ 2d 1461 affirmed the earlier case but does not deal with commercial success and practical utility. It states: "correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under §101," however, it does not apply to the current situation since there is no infringement of the current claimed invention. Furthermore, it is unclear how the claimed invention is going to be used by this pharmaceutical company. For instance, if the company is using the mouse for studying the function of the CX2 gene, it at most gives the claimed mouse a scientific utility,

which is different from the patentable utility for reasons discussed above. With regard to the sentence quoted from Lipscomb's Walker on Patents, the examiner cannot comment on it because it is unclear what context such statement was made. For example, what evidence should Applicants provide to establish sales and commercial demand? Is it a secondary evidence to some other requirement? A search of the book reveals that it ends at page 530, there is no page or paragraph 562. As such, this statement alone does not support that sale of this mouse to one company automatically gives the claimed mouse a patentable utility. Therefore, based on the utility requirement set forth in MPEP, the sale of the mouse to one company does not give the claimed mouse a patentable utility.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that this case law applies to the instant case. In the *Brana* decision, the court concluded that the mouse tumor models (leukemia cell lines were originally derived from lymphocytic leukemia in mice) represent a specific disease against which the claimed compounds were alleged to be effective. As such, the claimed compound has credible, substantial and specific utility. In *Brana*, the asserted utility meets the requirement of the statue because the claimed compounds are effective in a valid and specific mouse tumor model. However, in the instance case, the claimed knockout mouse does not have a credible, substantial and specific use because the specification does not teach what specific disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. The mere statement that the claimed mouse can be used to study diabetes and other metabolic disorder is not sufficient to establish a credible, substantial and specific utility for the claimed mouse. The phenotype of the

claimed mouse is decreased glucose level in blood after administration of glucose, which is opposite to a diabetic model, wherein the animal cannot metabolize glucose. As such, it cannot be used as a valid diabetic model. The specification fails to teach what other metabolic disorder the claimed mouse represents. The prior art is silent on the claimed mouse thus does not recognize any well-established utility for the claimed mouse. Moreover, the utility of using the claimed mouse to study CX2 function or association to the phenotype is not a credible, substantial and specific utility for reasons discussed above. Therefore, unlike *Brana,* the instant specification fails to provide a credible, substantial and specific utility for the claimed mouse.

In response to Applicant's argument with regard to the data presented in the specification, Applicant is reminded that the examiner does not doubt the statements made in the specification, but simply indicate that the specification does not provide sufficient teaching to support the asserted utility is credible, substantial and specific to the claimed invention. With regard to Applicant's argument that more than 10 mouse are used in each experiment, it appears to be contradictory to the data presented in Figure 4, wherein the number appears to be six. The examiner does not wish to comment on the credibility of the research and advanced education the Deltagen employees have received, which is irrelevant to the instant rejection.

Applicant is again reminded that the asserted utility of the claimed invention need to be credible, substantial and specific according to the 101 statue. The utility of studying CX2 function using the claimed mouse fails to meet this requirement (see reasons given above). With regard to Applicant's argument of predictability of

phenotype, although Applicant use gender, age and strain matched wild type controls, the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background gene, and other unknown mutations in the genetic background (see Crawley, pages 107 last paragraph through page 108 1st paragraph). Since C57BL/6 and various substrains of 129, two strains commonly used in ES cell and knockout generation, are unusual on many standard behavioral paradigms (see page 108, 2nd paragraph), (which are also used by Applicant for generating the CX2 domain gene knockout mouse), further characterization is required to make sure that the claimed phenotype is truly resulted from the inhibition of the CX2 domain gene. Although making a mouse with a null allele by a replacement vector usually knockout the gene, the phenotype is still unpredictable because it not only depends on the function of the endogenous gene but also what exogenous DNA the gene is inserted/replaced with, and where the exogenous DNA is inserted (see Scarff et al., 2003, Genesis, Vol. 36, page 149-157, specifically page 155, 1st col., 3rd paragraph). As such, further research is clearly required to establish an association between the CX2 and observed phenotype, thus further research is required before the claimed mouse can be used to study association of CX2 and the phenotype.

In response to Applicant's argument regard using the transgenic mouse comprising null-reporter allele to study the gene expression, Applicant is reminded that studying the expression of a gene of which the function is not known is not a substantial utility. Studying the expression of a gene for the purpose of exploiting said gene function is not a substantial utility because further research is required to determine said

gene function, and such gene expression pattern merely provides a clue for said gene function. The "clue" does not rise to the level of a substantial utility. Similarly, studying the expression of a gene for the purpose of determine how to use said transgenic mouse constitutes further research to determine how to use the claimed product, thus it does not provide a substantial utility to the claimed product. Therefore, the specification fails to teach a patentable utility for the claimed mouse.

For reasons given in the previous office action and above, the specification fails to disclose a credible, substantial and specific use for the claimed mouse and one skilled in the art would not know how to use the claimed mouse according to the embodiments disclosed by the instant specification. The rejection is thus applied to the newly presented claims 42-46 for same reasons as discussed in the previous office actions and above.

Claims 29-32, 36, 38-40 and 42-46 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to this rejection, Applicant argues that the claimed invention satisfied the utility requirement, thus, it also satisfy the enablement requirement.

The claimed invention lack patentable utility for reasons discussed in the previous office actions and above. Since Applicant did not respond to 112 1st rejection separately, this rejection is maintained for same reasons as discussed in the previous office actions. Newly added claims

42-46 are also rejected under 112 1st paragraph for same reasons as discussed in previous office actions.

Specification

The amendment filed 5/13/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The original specification discloses "a targeting construct prepared directly from a plasmid library using the methods described in pending U.S. Patent Application Ser No.: 08/971,310, filed on November 17, 1997, the disclosure of which is incorporated herein in its entirety" (see page 11, paragraph 2). The amendment filed on 5/13/05 amended the language to "using the methods described in U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816...which is incorporated herein in its entirety." Such amendment introduces new matter because the disclosure of "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816..." differs from the original disclosure and contains new information which was not disclosed in the original specification. Therefore, such amendment contains new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

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PATENT EXAMINER